Resistant hypertension (RHTN) is defined as the failure to achieve goal blood pressure (BP), despite adherence to maximally tolerated doses of an appropriate regimen of 3 antihypertensive agents, including a diuretic.1,2 Interest surrounding its evaluation, diagnosis, and treatment has gained significant momentum for the following several reasons: (1) the recognition that patients with true RHTN appear to lie at the extreme end of an already high-risk cardiovascular (CV) morbidity and mortality continuum3–5; (2) the acceptance that accurate estimates of the incidence and prevalence of RHTN remain largely unknown5–8; (3) the need to establish robust prognostic associations to benchmark the degree of benefit gained from timely and consistent management; (4) the need to define the optimal pharmacotherapeutic regimen for RHTN; (5) evidence that RHTN may, at least in part, be mediated by chronic activation of the sympathetic nervous system (SNS); and (6) the subsequent emergence of percutaneous sympathetic denervation of the renal arteries—a novel intervention that could stimulate a paradigm shift in the way we manage not only treatment-resistant systemic HTN, but also a myriad of pathophysiological entities associated with chronically augmented SNS activation.10

In this review, we focus on the evolution of renal sympathetic denervation (RSDN) therapy; its role in the management of RHTN; current trial data; the wider application of renal denervation in the treatment of heart failure (HF), arrhythmia, and the metabolic syndrome; and emerging technologies for this potential device-based standard of care.

A Novel Application for an Established Concept

The renal SNS comprises a dense network of postganglionic efferent fibers that run from the hypothalamus to the kidney via pre- and paravertebral sympathetic ganglia (T10–L2).11,12 Afferent renal sympathetic nerves emerge predominantly from the renal pelvic wall, where mechanoreceptors respond to stretch and chemoreceptors detect renal ischemia and alterations of the biochemical milieu.10 From the ipsilateral dorsal root ganglia (T6-L4), the afferent pathways then ascend to the autonomic centers in the brain10 and to the contralateral kidney, thereby allowing cross-regulation of renal hemodynamics in response to changes in ipsilateral flow and function.12 Both the efferent and afferent fibers follow the course of the renal artery to each kidney and lie primarily within the adventitia, the only location where these nerves travel together (Figure 1).

Chronic augmentation of central sympathetic drive plays a pivotal role in sustaining elevated BP.14 Stimulation of renal efferents leads to an increase in renin secretion by the juxtaglomerular apparatus mediated by β1-adrenoceptors, direct sodium reabsorption by epithelial tubular cells through combined β1- and α1-adrenoceptor action, and vascular smooth cell contraction leading to an attenuation of renal blood flow, mediated by α1-adrenoceptors.19,15–17 Moreover, the enhanced renin release activates the renin–angiotensin–aldosterone system; an overlap in the neurohumoral axis leading to further volume expansion mediated by aldosterone and increased sympathetic activation, vasoconstriction, and water absorption (via antidiuretic hormone secreted by the pituitary) stimulated by angiotensin II.18 Signals from sensory renal afferents help to regulate whole body sympathetic tone through modulation of posterior hypothalamic activity, which in turn positively feeds back to further sustain renal efferent sympathetic activity.19,20 Figure 2). In essence, therefore, disruption of the sympathorenal axis could selectively reduce the contribution of the kidney to central sympathetic drive. Such an intervention would thus seem an attractive, and indeed logical, therapeutic outlet for managing RHTN.

In the 1930s, surgical attempts to modify SNS activity led to the adoption of radical nonsympathectomy, later followed by thoracolumbar splanchnectionctomy, as a means of treating severe (or malignant) HTN.21–25 The so-called Smithwick procedure did not target the kidneys specifically but nonetheless resulted in renal denervation above and below the diaphragm. Despite a high-operative mortality, prolonged...
postoperative convalescence, often disabling complications (eg, severe orthostatic hypotension, anhidrosis, atelectasis, intestinal disturbances, erectile dysfunction, and urinary and fecal incontinence), and inconsistent reductions in BP, patients were willing to have the procedure because malignant HTN had virtually 100% 5-year mortality if left untreated.21 Although driven into obscurity once orally active antihypertensives became available in the 1960s,26,27 the marked reductions in BP levels and improvements in survival afforded by the technique clearly demonstrated the intrinsic relationship among the SNS, the kidneys, and BP regulation. It was shown to stimulate diuresis, natriuresis, and reduce renin release without adversely affecting other measures of kidney function, such as renal blood flow and glomerular filtration rate.21-25 Human kidney transplantation, a procedure in which the native sympathetic connections of the transplanted kidney are severed, elegantly highlights the ability of the denervated donor kidney to maintain electrolyte balance and volume homeostasis within the recipient.28,29 Furthermore, the consistent reduction in BP and systemic vascular resistance reported after bilateral nephrectomy in patients with end-stage renal disease outline the potentially harmful role of renal afferent neurogenic stimuli emanating from the diseased kidneys and provide yet more persuasion for targeting the renal SNS.15,30

Five decades later, the challenge has been to condense the pathophysiological principles borne out of surgical sympathectomy into a minimally invasive procedure that can selectively
modulate renal SNS activity, without disrupting the innervation of other abdominal or pelvic organs. Supported by data from several experimental models of HTN alongside preclinical confirmation of vascular safety and healing response,\textsuperscript{31–34} percutaneous RSDN has emerged as a viable method of abrogating sympathetic hyperactivation.

Will Demand Match the Potential Supply?

The true incidence and prevalence of RHTN remain elusive.\textsuperscript{2,5–8,35} In the Health Survey for England, 20% of hypertensive patients had uncontrolled BP, despite the administration of at least 3 drugs, which corresponds to a RHTN population of between 0.5 and 1 million individuals in England alone.\textsuperscript{36} A survey of the Kaiser Permanente Colorado and Northern California healthcare systems found the incidence and prevalence of RHTN to be 1.9% and 16.2%, respectively.\textsuperscript{5} The California healthcare systems found the incidence and prevalence of RHTN to be \( \approx 1.9\% \) and \( \approx 16.2\% \), respectively.\textsuperscript{5} The results were further strengthened by exclusion of patients with apparent RHTN and inclusion of a large and ethnically diverse population. Patients with RHTN were almost 50% more likely to experience an adverse CV event over a median 3.8-year follow-up period when compared with those patients controlled on \( \leq 3 \) medications.\textsuperscript{5} The increased risk was predominantly caused by chronic kidney disease (CKD). Furthermore, the global REACH Registry found that \( \approx 13\% \) of hypertensive patients with or at high risk of atherothrombosis had RHTN and with that a markedly higher risk of stroke and hospitalization for HF.\textsuperscript{2} The true long-term prognosis of patients with RHTN is, however, yet to be accurately defined. Post hoc analysis of large clinical outcome trials of antihypertensive medication suggests the prevalence of RHTN could be as high as 35%,\textsuperscript{37–42} Amalgamation of these trial results with more contemporary observational findings would make the true prevalence of RHTN rising markedly from 600 million in 1980 to an estimated 1 billion in 2008, the number of individuals eligible for, at least, a preliminary assessment for RSDN therapy is potentially vast.\textsuperscript{43}

Translating the Data into Clinical Practice

In anticipation of the widespread uptake of RSDN, several UK authorities have advocated a multidisciplinary team approach, with best practice encompassing an individualized patient-centered discussion and subsequent assessment to confirm true RHTN, followed by a coordinated ongoing care package provided by the physician with an interest in HTN and the endovascular interventionalist.\textsuperscript{44,45} Similar position papers have been proposed by the European Society of Hypertension and a French conglomeration of key stakeholders.\textsuperscript{46,47}

The current evidence base relies predominantly on experience with the Symplicity Renal Denervation system (Medtronic Inc, Minneapolis, MN), which has evolved from an 8F to 6F catheter introduced via the femoral artery—there is no radial system at present. A case report (\( n=1 \)), an open-label feasibility study (Symplicity HTN-1: \( n=153 \) at 2-year follow-up), and an unblinded randomized controlled trial (Symplicity HTN-2: \( n=82 \) at 1-year follow-up) form the modest body of published data supporting the use of this device.\textsuperscript{48–52} It received its European CE mark in 2010 but remains limited to investigational use in the United States.

Patient Selection

Both the Symplicity HTN-1 and HTN-2 trials defined RHTN as an office systolic BP \( \geq 160 \) mm Hg (or \( \geq 150 \) mm Hg in type 2 diabetes mellitus) for trial entry, based on an average of 3 office readings.\textsuperscript{48,50} Although no overall unifying definition currently exists for RHTN, goal BP has been set at \( <140/90 \) mm Hg by the majority of national and international guidelines,\textsuperscript{2,3,5,4} with potentially lower targets for patients with diabetes and those who manifest CV, cerebrovascular, or renal disease. Moving forward, the arbitrary BP threshold used in the HTN-1 and HTN-2 trials could have overlooked a significant section of the real-world RHTN cohort.

Apparent or pseudo-RHTN, defined as inadequate BP control in a patient who does not have true RHTN but is receiving appropriate treatment, must first be excluded (Table 1). Up to one third of patients, defined as having RHTN according to office BP recordings, are later found to manifest a white coat effect (ie, a persistently elevated office BP but a normal home or ambulatory daytime average BP of \( <135/85 \) mm Hg).\textsuperscript{3} This serves to emphasize the importance of using ambulatory BP monitoring to confirm a true RHTN diagnosis.\textsuperscript{2,4,44,53} A white coat effect should be suspected in any individual with persistently elevated office BP readings but no signs of target organ damage or signs/symptoms of overtreatment, such as postural hypotension, dizziness, or syncope.\textsuperscript{5} In HTN-2, a 2-week baseline evaluation period was used to establish BP patterns with twice-daily home BP monitoring and a daily medication log to confirm treatment concordance before formal randomization. Despite the opportunity to use these out-of-office BP recordings, the investigators restricted their RHTN diagnosis to the mean of office BP measurements. This potentially limits the generalizability of the trial results. Current guidelines all regard ambulatory BP monitoring confirmation of RHTN to be an essential component of RSDN eligibility.\textsuperscript{44–47}

Consideration of treatment adherence is especially important in RHTN evaluation. Recent medication changes or dose

<table>
<thead>
<tr>
<th>Table 1. Factors Associated With Pseudo- or Apparent Resistant Hypertension\textsuperscript{3}</th>
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<tbody>
<tr>
<td><strong>Factors associated with the patient</strong></td>
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<tr>
<td>White coat effect</td>
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<tr>
<td>Cuff-related artifact (especially in elderly patients)</td>
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<td>Poor patient adherence to treatment</td>
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<tr>
<td>Side-effects of antihypertensive medication</td>
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<td>Complicated dosing regimens</td>
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<td>Inadequate patient education</td>
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<tr>
<td>Memory or psychiatric issues or poor cognition</td>
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<tr>
<td>Difficult relationships between patient and healthcare providers</td>
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<td>Costs of medication (will vary according to healthcare system)</td>
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<td><strong>Factors associated with the physician</strong></td>
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<td>Poor office BP measurement technique</td>
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<td>Physician inertia</td>
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<td>Inadequate dosages of antihypertensive medication</td>
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<tr>
<td>Inappropriate choice of antihypertensive combinations</td>
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<td>Poor communication and lack of desire to invest in patient education</td>
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BP indicates blood pressure.
adjustments should be given time to work, this can take up to a month to take effect, before reassessing for RSDN. In HTN-2, inclusion criteria included a stable treatment regimen of ≥3 antihypertensives before randomization, which prevented any change in drug or dose 2 weeks before randomization and maintenance of the same baseline combination for at least 6 months post-RSDN to avoid adjustments confounding the results.50

Patients in HTN-1 and HTN-2 were taking an average of 4.7 and 5.2 antihypertensive medications, respectively. Although an essential criteria for RHTN (given the predominance of volume and sodium overload in many of these patients), diuretic therapy was not taken by all trial participants (HTN-1, 95% and HTN-2, 89% at baseline). This, perhaps, not only reflects the heterogeneity of the population under investigation, physician inertia, or intolerance to medication, but also a lack of guidance on specific RHTN antihypertensive regimens.44,50–52 UK guidelines now stipulate patients should have uncontrolled BP, despite treatment with a specific A+C+D regimen (Figure 3) to be eligible for RSDN; the French recommendations are similar.44,45,47,53

There is currently no robust evidence to define the most clinically effective fourth or fifth line agent to improve BP control in RHTN. Moreover, it is unlikely that any 1 class of drug will suit every patient.56 The best available, although weak, evidence supports the use of low-dose spironolactone (ie, 25 mg once daily, increasing to 50 mg once daily) as the preferred fourth line agent, if the blood potassium level is ≤4.5 mEq/L.57–62 This is further advocated in European RSDN guidelines.44,46,47 In HTN-1, only 22% of patients were taking an aldosterone antagonist at baseline62 and only 17% in HTN-2.50 These trials, however, were initiated in 2007 and 2009, respectively, predating the recent push toward spironolactone.57,60,62

Efforts should also be made to ensure that the full range of lifestyle modifications have been exhausted and an inquiry be made in to the use or potential misuse of exogenous substances/competing medications and, where possible, the offending agents discontinued, minimized, or substituted appropriately (Table 2).

Secondary Causes of Hypertension
Excluding patients with known secondary causes of HTN is routine at present and was actively performed in HTN-1.48,51 The protocol for HTN-2 excluded type 1 diabetes mellitus but did not explicitly exclude those with a known secondary cause, the reason behind the shift in recruitment protocols is unclear.50 Studies indicate 5% to 10% of patients with RHTN have an underlying secondary cause,63,64 the most common being hyperaldosteronism, CKD (either the cause or consequence of chronic, poorly controlled HTN), renal artery stenosis (RAS), and obstructive sleep apnea. Neither HTN-1 nor HTN-2 mandated specific investigations to eliminate hitherto undiagnosed secondary causes of RHTN. This potentially limits the generalizability of their findings. Any investigation pathway for secondary causes of HTN should include a focused history, thorough physical examination, biochemical evaluation, and noninvasive imaging (Table 3).

Preprocedure Anatomic Considerations
Having identified patients with true RHTN, the next step is to perform mandatory imaging of the renal vessels to ensure suitability for catheter-based RSDN. The following should be excluded:

Table 2. Factors Contributing to Resistant Hypertension1

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
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<tr>
<td>Obesity</td>
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<td>Excess alcohol intake</td>
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<tr>
<td>Excess dietary sodium</td>
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<tr>
<td>Cocaine and amphetamines use</td>
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<tr>
<td>Drug-related causes</td>
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<td>Nonsteroidal anti-inflammatory drugs</td>
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<tr>
<td>Contraceptive hormones—combined oral contraceptives are more often associated with elevated BP, whereas menopausal hormone therapy has minimal effects on BP</td>
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<tr>
<td>Adrenal steroid hormones</td>
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<tr>
<td>Sympathomimetic agents (nasal decongestants, diet pills)</td>
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<tr>
<td>Erythropoietin, cyclosporine, and tacrolimus</td>
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<tr>
<td>Licorice—suppresses the metabolism of cortisol</td>
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<tr>
<td>Herbal supplements (ephedra, ma huang, bitter orange, etc)</td>
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<tr>
<td>Volume overload</td>
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<tr>
<td>Progressive renal insufficiency</td>
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<tr>
<td>High-salt intake</td>
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<tr>
<td>Inadequate diuretic therapy</td>
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BP indicates blood pressure.
Table 3. Assessment for Secondary Causes of Resistant Hypertension

Hyperaldosteronism: a pure imaging-based strategy to detect adrenal hyperplasia or adenoma will generate false positives, as these can be common findings on computed tomography (CT) or magnetic resonance imaging (MRI). Initial biochemical screening is advised followed by imaging or selective venous sampling. β-Blockers suppress plasma renin levels and should be stopped and blood tested for the renin:aldosterone ratio. A patient taking A+C+D, assuming they are taking their medication, should have an elevated renin level and should be investigated if they have a low renin, as it is highly suggestive of potential secondary causes.

Intrinsic renal disease: biochemical analysis, urinalysis, and some form of imaging, such as CT.

Renovascular disease: renal arterial Duplex scanning or CT/MRI scanning are useful modalities. Note young females and the possibility of fibromuscular dysplasia.

Pheochromocytoma: rare but should be excluded with 24-hr urine testing.

Cushing’s syndrome: rare but should be suspected in overweight patients and can be excluded with 24-hr urinary cortisol.

Coarctation of the aorta: a normal clinical examination and chest radiograph make the diagnosis unlikely and negate the requirement for advanced imaging of the aorta.

Obstructive sleep apnea: inquiry into symptoms of profound daytime sleepiness and disturbed sleep should be routine. The Epworth Sleepiness Scale and overnight pulse oximetry may be helpful as is a history from the patient’s spouse or partner.

1. Main renal arteries <4 mm in diameter and <20 mm in length before any major branch bifurcation.
2. Dual or multiple renal arterial anatomy.
3. Significant ostial or body renal arterial atheroma/calcification (RAS >50%).
4. Fibromuscular dysplasia.

Currently, there is no consensus as to which renovascular imaging modality should be used. Duplex ultrasound lacks sufficient resolution, whereas the ionizing radiation from CT angiography precludes serial imaging. There is also the issue of contrast-induced nephropathy when using CT angiography and gadolinium-enhanced MR angiography, especially in a cohort with enhanced sensitivity to renal injury. Much will depend on local protocols, institutional expertise, and equipment availability.

Patients who have had previous renal artery intervention are not eligible for RSDN, although there has been an isolated case report in which bilateral RSDN was performed in a patient with renovascular HTN, having previously received stenting to the right and balloon angioplasty to the left renal artery. Dual or multiple renal arteries can each be treated, but only vessels supplying at least 25% of the kidney are likely to have significant sympathetic innervation. The infrarenal abdominal aorta should ideally be free of significant pathology, such as atherosclerotic plaques and aneurysm. Patients with suboptimal anatomy that excluded them from HTN-2 enrollment, but went on to receive RSDN therapy, were entered in to the Global Symplicity Registry (ClinicalTrials.gov Identifier: NCT01534299). This will consecutively enroll a minimum of 5000 patients from more than 200 sites worldwide to determine the real-world durability of effect and safety of the device.

Renal Function

Patients required preserved renal function (estimated glomerular filtration rate [eGFR] >45 mL/min per 1.73 m²) to enter both HTN-1 and HTN-2. In the 10 HTN-1 patients in whom data were available at 2 years postprocedure, the eGFR fell by −16.0 mL/min per 1.73 m². Half of these had spironolactone or other diuretic added to their multidrug regimen after the first year, whereas those who did not demonstrated a −7.8 mL/min per 1.73 m² change in eGFR. No individuals developed stage IV CKD (15–29 mL/min per 1.73 m²), required dialysis, or demonstrated a significant increase in serum creatinine. At 6-month follow-up in HTN-2, there was no change in renal function in either treatment arm, although 2 RSDN patients did have a >25% reduction in eGFR. At 1 year, there was still no change in eGFR in the 45 patients originally assigned to RSDN or the 35 patients that crossed over to RSDN after 6 months. A small sample size makes it difficult to determine whether any compromise in eGFR post-RSDN was secondary to the deleterious consequences of the underlying hypertensive state, exposure to contrast media, diuretic sensitivity heightened by RSDN rendering the kidney less able to autoregulate against falls in perfusion pressure, an adverse effect on renal hemodynamics, or damage to the renal artery during the procedure, for example, prolonged spasm or dissection, or delayed development of RAS. Approximately one third of patients in HTN-1 and HTN-2 had type 2 diabetes mellitus, which might also account for the sporadic decline in renal function, although no specific subset analysis was performed.

The attenuation of renal arterial blood flow in patients with CKD may complicate the RSDN procedure by restricting the dissipation of heat during ablation. In a pilot study involving 15 RHTN patients with stage 3 to 4 CKD (mean eGFR, 31 mL/min per 1.73 m²), irrespective of the contrast media used, eGFR remained unchanged 3 and 6 months after bilateral RSDN. In the 5 patients with results out to 12 months, however, eGFR fell precipitously in 1 and gradually in the remainder. Until data from much larger cohorts of patients with pre-existing renal dysfunction is available, it would seem prudent to restrict the performance of RSDN to those with preserved renal indices in line with current national and international consensus.

Catheter-Based Renal Sympathetic Denervation

General Principles

A short selective guide catheter is placed in each renal artery under fluoroscopic guidance and heparin or bivalirudin anticoagulation. With the Symplicity system, a flexible radiofrequency ablation catheter is advanced to the distal renal artery, with typically 4 to 6 ablations performed serially, in a distal to proximal fashion in the classical helical pattern, although it is not clear just how essential the spiral pattern really is (Figure 4). Each ablation is positioned and performed individually taking 2 minutes each. During energy delivery, the tip of the
catheter induces heating between 70°C to 90°C in the subjacent tissue up to 4 mm distant. This is the primary treatment effect, with progressive thermal destruction of the neural tissue that resides in the adventitia of the renal artery (Figure 1), with blood flow cooling the intima to minimize endothelial injury. Vessels with lumens obstructed by atheroma or calcification should therefore be avoided; both will physically increase the distance between the catheter tip and the nerve bundle, potentially dampening the effect of the thermal energy emitted. The neural tissue bundle contains a proportion of C fibers, exposing the patient to the risk of extreme discomfort during each ablation unless adequate analgesia and anesthesia are routinely used. Conscious sedation with an opiate and benzodiazepine cocktail at baseline, which can then be topped-up for breakthrough pain, is the preferred method.

Small arterial side branches and the carina of bifurcations must be avoided because the catheter tip will rapidly heat due to loss of cooling blood flow. Ablations should also be a minimum of 10 mm from the kidney end of the vessel. Avoidance of the ostia is recommended, but in practice this often represents a viable treatment area in short vessels. Each ablation should be separated by 5 mm to mitigate the potential risk of RAS. Catheter instability can arise from deep respiratory movement, forceful cardiac contractions, or ablation at the level of the ostia. Ensuring adequate analgesia during the procedure can minimize such movement.

Biomarkers of Success
A robust biomarker of successful denervation is currently unavailable. BP will typically take weeks or months to fall postprocedure. Radiologically, good catheter placement and contact with the vessel wall is important; this is judged from the fluoroscopic appearance (Figure 4) and the electrophysiological data from the generator console, measured as the impedance value in Ohms. The temperature of the tip during radiofrequency ablation is also recorded to ensure delivery of energy up to a maximum of 8 watts. The process is largely automated; comprehensive safety algorithms abort any treatment cycle if significant deviations arise. During the ablation, the impedance of the catheter-based circuit decreases as tissue is heated. The precise reason for this is not fully clear but likely represents release of intracellular electrolytes into the interstitium, thereby reducing electric resistance in the local tissue. The drop in impedance forms the main therapeutic target during each treatment cycle, with a drop of >10% in absolute terms considered indicative of a successful ablation. Impedance can vary markedly between patients, thus it is the change in impedance at each ablation, rather than the baseline value, that is important.

Complications of the Procedure

Vessel Spasm
This is common during ablation, with smaller vessels approaching 4 mm being more prone, presumably attributable to greater circumferential heating with each ablation. Procedure guidance recommends routine nitrate instillation into the vessel pretherapy, but in some centers this practice is avoided because hypotension can be profound in hypertensive patients with a history of chronic diastolic ventricular stiffness. In the authors’ experience, intra-arterial nitrates, verapamil, and diltiazem have all been used with success, and persistent flow-limiting spasm seems to be extremely rare. Patches of edema along the vessel are common and referred to as denervation notching which these invariably resolve (Figure 5).

Anesthetic Issues
Conscious sedation without an anesthesiologist must be very carefully implemented with the aid of continuous patient monitoring. Fluctuations in systemic BP during the procedure are also common and can be mitigated by careful use of nitrates, good analgesia, and crystalloid infusions to maintain plasma volume. Transient bradycardia has been documented but almost always responds to atropine if profound; there are no published reports of temporary pacemaker use.

Renal Artery Dissection
Reported cases of dissection requiring stent placement are extremely rare (<1 in 1000), and perforation has yet to occur. A single patient in HTN-1 had dissection on insertion of the treatment catheter, which was then treated by stenting without further sequelae. The need for prolonged balloon angioplasty and deployment of a stent will be dictated by the extent of the vessel injury. Denervation has been pursued in the contralateral renal artery once the situation in the affected artery has been stabilized.
Renal Artery Stenosis

The HTN-1 and HTN-2 trials reported 1 patient with possible progression of pre-existing RAS in a treated vessel on angiographic/MRI-based follow-up, but overall global experience shows this to be an extremely rare occurrence. However, there has been limited systematic imaging of renal denervation patients, and as such the true incidence may be higher than currently appreciated.

Aftercare and Follow-Up

Patients are typically kept in bed for 12 hours and discharged the next day with instructions to continue taking all their antihypertensive medications. No consensus exists regarding dual antiplatelet therapy, but the intimal denudation associated with the procedure suggests a brief course of clopidogrel may reduce the small risk of arterial thrombus.

Patients should be followed up monthly thereafter, with periodic confirmation of ambulatory BP monitoring changes. This approach often allows down-titrations of antihypertensive therapy, but the intimal denudation associated with the procedure suggests a brief course of clopidogrel may reduce the small risk of arterial thrombus.

Because clinical experience remains limited, it is difficult to be entirely prescriptive of the medical surveillance that should be instituted postintervention. French consensus advocates surveillance with CT angiography at 12 and 36 months. This is likely to pose too high a radiation risk and might be considered unnecessary in patients who are clinically stable. Renal artery ultrasound at 6 months to rule out RAS may be reasonable. Alternatively, non–contrast-enhanced MR angiography with ECG and respiratory gating uses fast steady-state gradient echo imaging to obtain high-resolution angiographic images, circumventing the need for a contrast agent. Other RSDN position papers are no more prescriptive on postprocedural renal imaging, reflecting the current lack of robust longitudinal data.

Importance of the HTN-3 Study

Results from HTN-1 demonstrated a durable reduction in office BP of −33/−19 mm Hg (P<0.01) in 24 patients (original cohort, n=143) out to 36 months. Of note has been the response rate to RSDN, although this in part reflects whether a response, defined as a systolic BP fall of ≥10 mm Hg, is sufficient for an invasive procedure. Response has been reported as 58% at 3 months, 64% at 1 year, and 82% by 2 years in HTN-1, the salient message being an eventual response of initial nonresponders over time. However, interpretation of this data is complicated by potential comitant medication changes and the lack of more objective ambulatory data. There may indeed be a cohort of initial nonresponders who could well be slow responders to denervation, although it remains unclear what the pathophysiological basis for this finding is. Indeed the distance of perirenal nerves from the lumen of the renal artery follows a normal distribution ranging from 0.5 mm through to >10 mm (mean, 2.0–4.0 mm), and so there is no guarantee that the energy from each ablation will successfully reach a nerve bundle and that the treated renal nerve fully extends to the kidney; this could in part explain nonresponsiveness to RSDN therapy and underlines the need to identify specific predictors of procedural success other than high baseline BP, which is not specific enough to enhance patient selection.

The 18-month results for HTN-2 revealed a −32/−12 mm Hg reduction in office BP (n=43) in those originally randomized to RSDN and a −28/−11 mm Hg fall in those crossing over to the RSDN arm after 6 months (n=31). Numerically, these results are impressive, although enthusiasm has been tempered and cynicism fuelled by the more modest reduction of approximately −10 mm Hg of systolic BP when ambulatory recordings were available.

Midterm results from HTN-1 and HTN-2 should serve to diffuse the argument for reinnervation of efferent and afferent nerve fibers after RSDN. It remains uncertain, however, what effect, if any, a renewed motivation for lifestyle modification and medication adherence could have contributed to this sustained BP reduction in patients, not only enthused by the positive results from RSDN, but also monitored more closely in an artificial trial environment. Importantly, follow-up was incomplete in both HTN-1 and HTN-2, and changes to antihypertensive regimens were not monitored after the 6-month postprocedure watershed.
Renal norepinephrine spillover (measure of renal efferent activity), total body norepinephrine spillover (measure of central sympathetic drive via the renal afferent pathway), and microneurography (measure of muscle sympathetic nerve activity) are metrics that could have been used to evaluate the durability of effect, but these have not been reported. A recent case series of 12 patients with RHTN receiving RSDN therapy did not, however, demonstrate a change in resting muscle sympathetic nerve activity 3 to 6 months postprocedure. Furthermore, the open-label designs of both HTN-1 and HTN-2 make them susceptible to expectation, performance, and evaluation biases, particularly when the primary outcome measure in HTN-2, seated office BP, was not recorded blind to treatment assignment. The patient cohorts in HTN-1 and HTN-2 were also predominantly whites (>95% for both trials) and obese, making it difficult to extrapolate their findings to a broader hypertensive population.

Consequently, Symplicity HTN-3 (ClinicalTrials.gov Identifier NCT01418261) was designed to overcome several of the perceived methodological limitations of HTN-1 and HTN-2. It is a prospective, randomized, masked procedure, single-blind trial that will be enrolling 530 patients in a 2 (treatment):1 (control) design at ≈90 sites within the United States. Patients will be blinded, to the extent possible (through conscious sedation, sensory isolation, and lack of familiarity with the RSDN procedure and its duration), by means of a sham control procedure as will predesignated BP assessors, thereby providing the first truly controlled assessment of this technique and minimizing confounding from expectation and evaluation bias, respectively. The sham control is a renal angiogram, which the patient would have required anyway before randomization. A crossover from the control arm to RSDN at 6 months is allowed if the patient continues to meet the inclusion criteria, and hence all randomized patients have the opportunity to be treated, circumventing any ethical concerns (Figure 6).

There is a rigorous screening process that comprises a patient home diary to confirm compliance with pharmacotherapy and ambulatory recordings. An ambulatory average systolic BP <135 mm Hg will exclude patients with white coat HTN. Additionally, patients must be treated with ≥3 optimally dosed antihypertensive medications from different, complementary classes, one of which must be an appropriately dosed diuretic. There is, however, no mandated use of an aldosterone antagonist as a fourth line agent. Routine assessment for RAS at 6 months will be performed. There has been a concerted effort to exclude patients with a secondary cause of RHTN. All patients will be maintained on their baseline antihypertensive regimen for the 6-month follow-up period unless extraordinary clinical circumstances justify an alteration. All patients, irrespective of intervention assignment, will be followed for 3 years postrandomization.

Potential Benefits of Renal Denervation on Disease States Driven by Chronic Sympathetic Hyperactivation

The putative ability of RSDN to attenuate central sympathetic output has stimulated a potential broadening of its application to other disease states driven by chronic sympathetic hyperactivation. In contrast, RSDN seems not to effect chronotropic competence adversely during exercise. Small studies have also shown RSDN to dampen sympathetic cardiac autonomic tone, which may have a beneficial protective effect in those patients at high CV risk. Small-scale trials of RSDN in HF are underway. SYMPLICITY-HF (ClinicalTrials.gov Identifier: NCT01392196) is designed to evaluate the safety and physiological response to RSDN in ≈40 patients with chronic HF and renal impairment. In the REACH Pilot study, bilateral RSDN was performed in 7 consecutive HF patients (New York Heart Association III and IV) on maximal recommended pharmacotherapy. RSDN was safe and did not lead to any hypotensive sequelae (mean clinic BP at baseline was 112/65 mm Hg) or adverse effects on renal function during a 6-month follow-up. RSDN significantly improved 6-minute walk test indices (Δ=27.1±9.7 m; P=0.03) and provoked a strong trend toward moderation of HF medication.

RSDN could also act as an adjunct to the management of arrhythmias. Sudden death, often caused by ventricular tachyarrhythmias, is common in patients with HF. Anecdotally, cases suggest that RSDN might be effective in controlling such electrical storms. Whether this is because it reduces cardiac sympathetic activity or because it reduces vascular

HF and Arrhythmias

Figure 6. SYMPLICITY HTN-3 trial flow. AMBP indicates ambulatory blood pressure monitoring; BP, blood pressure; HTN, hypertension; and SBP, systolic blood pressure. Reproduced from Kandzari et al80 with permission of the publisher. Copyright © 2011, John Wiley & Sons Inc.
Table 4. A Snapshot of Emerging Novel Renal Denervation Technology

<table>
<thead>
<tr>
<th>Company</th>
<th>Device Name</th>
<th>Specifications</th>
<th>Phasic Development</th>
<th>Potential Advantages</th>
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<tbody>
<tr>
<td><strong>Radiofrequency ablation</strong></td>
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<tr>
<td>Covidien-Maya, Mansfield, MA</td>
<td>One-Shot, CE mark: February 2012</td>
<td>Helical silver monopolar electrode mounted on a noncompliant balloon inflated to &lt;1 atm</td>
<td>RHAS Trial experience: Single-center, data reported on 8 patients. Median procedure time 17 min, average reduction in office BP at 6 mo of −42/−15 mmHg. No major adverse events</td>
<td>Single therapy delivery means reduced procedure times (2 min) and consistency of treatment</td>
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<td>Irrigation holes placed alongside spiral electrodes</td>
<td>RAPID Trial: 50-patient, multicenter, single-arm study in Europe and New Zealand – first patient enrolled May 2012</td>
<td>Less dependent on operator experience/technique</td>
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<td></td>
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<td>Delivered by 0.014 inch guide wire</td>
<td>RAPID-2: Postmarket registry announced</td>
<td>Balloon inflation increases stability and electrode contact</td>
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<td>7F device currently</td>
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<td>Irrigation hole cooling protects nontreated parts of the artery</td>
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<tr>
<td><strong>Boston Scientific Corp, Natick, MA</strong></td>
<td>V2 Renal Denervation System, CE mark: May 2012</td>
<td>Low-pressure (3 atm) noncompliant balloon catheter with RF gold bipolar electrodes and thermistors mounted on the external surface</td>
<td>REDUCE-HTN Pilot: Successful pilot study of 13 subjects at 5 centers led to CE mark approval</td>
<td>Rapid treatment times (30 s per ablation)</td>
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<td>Balloons sized for 3–7 mm vessels</td>
<td>REDUCE-HTN: Postmarket approval surveillance study planning to recruit 120 subjects at 24 sites currently underway</td>
<td>Gold electrodes maximize thermal and electric conductivity and radio-opacity</td>
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<td>Small diameter balloons allow treatment in accessory renal arteries (≤4 mm)</td>
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<tr>
<td><strong>Medtronic, Minneapolis, MN</strong></td>
<td>Multi-electrode RF Renal Denervation System</td>
<td>4-electrode catheter delivering simultaneous energy</td>
<td>FIM Phase I complete (9 patients) in October 2012</td>
<td>Reduced ablation time (60 s per artery)</td>
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<td>FIM Phase II (up to 50 patients) currently underway</td>
<td>Consistency of RF energy application</td>
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<td>Conformable and nonocclusive</td>
<td>A final iteration of the device is not yet available</td>
<td>Potential to treat a wide range of renal artery anatomies</td>
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<td></td>
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<td>Monorail delivery</td>
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<td><strong>Ultrasound</strong></td>
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<tr>
<td>Kona Medical, Bellevue, WA</td>
<td>Surround Sound System</td>
<td>External delivery of ultrasound energy</td>
<td>Unlikely to move forward with the catheter approach beyond initial clinical data acquisition</td>
<td>Energy field ablates renal nerves without impacting on vascular structures</td>
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<td>First generation: Low profile intravascular catheter for targeting and tracking; used for collection of baseline dosimetry and preclinical safety data before initial trials</td>
<td>More complete ablative field through external ultrasound delivery</td>
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<td>Second generation: Fully noninvasive system</td>
<td>Can overcome issue of variable renal artery anatomy</td>
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<td>Energy can be emitted circumferentially</td>
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<tr>
<td>ReCor Medical Inc, Menlo Park, CA</td>
<td>PARADISE, CE mark: December 2011</td>
<td>Transducer in a low-pressure balloon that permits uniform circumferential denervation using ultrasound energy</td>
<td>REDUCE Trial: FIM (n=15), 2 patients with severe RAS in suboptimal cooling flow rate group (n=8 at 6 mo); no cases of RAS in subgroup with increased cooling flow rate (n=7 at 6 mo); office BP reduced by −33/−17 mmHg at 6 mo (n=15) 93% responder rate</td>
<td>Energy field ablates renal nerves without impacting on vascular structures</td>
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<td>More complete ablative field through external ultrasound delivery</td>
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(continued)
tone and ventricular loading is uncertain, but benefits have been reported within hours of the procedure. RSDN has also been suggested as a possible adjunct to the management of atrial fibrillation in a model of obstructive sleep apnea and when combined with pulmonary vein isolation, but this is pure speculation at present.

**Metabolic Syndrome**

Many hypertensive patients are overweight, have abnormal insulin/glucose metabolism, left ventricular hypertrophy, and obstructive sleep apnea. Afferent RSDN may improve skeletal muscle blood flow secondary to arteriolar dilatation, leading to better capillary flow and myocyte perfusion. Theoretically, this could lead to improved insulin sensitivity. Reductions in sympathetic activity could also reduce gluconeogenesis. A pilot study of 50 RHTN patients suggested rapid improvement in insulin resistance within 4 weeks of receiving RSDN. This was accompanied by a marked reduction in BP and a downward trend in weight. However, this study was small, not properly randomized (n=26 went on to HTN-2 trial enrollment), and there may have been important differences in baseline characteristics, despite not being statistically significant because of the small study size. Another study had similar findings and also noted an improvement in obstructive sleep apnea.

Sustained BP control is expected to lead to a reduction in left ventricular hypertrophy and no alternative mechanism need be invoked, although reduction in cardiac sympathetic activity could have an additive effect mediated either by improving insulin resistance or by reducing α-adrenergic receptor activity. A trial comparing the effects of RSDN on left ventricular function in 28 patients with RHTN versus a control group of 18 patients suggested left ventricular ejection fraction may increase and diastolic function may improve. If this constellation of effects is confirmed, then RSDN might be expected to prevent or delay serious complications of HTN, such as HF.

**Emerging Renal Denervation Technology**

Published data and global experience in more than 4500 patients have thus far shown catheter-based renal denervation to be safe and well tolerated. This has stimulated the development of new RSDN technologies, currently involving more than 60 companies. All are at various iterative stages and use different means of inducing perivascular renal denervation (Table 4; Figure 7).

Factors central to the future success of any novel RSDN technology are as follows: (1) efficacy and safety supported by robust randomized data; (2) the penumbra of energy or transmurality of the device, the extent to which energy can be circumferentially distributed to penetrate the adventitia or (3) the ability to target perivascular sympathetic, and not parasympathetic, nerves, or C fibers specifically. Ideal characteristics might also include the following: radial plus femoral access or perhaps a totally noninvasive procedure altogether; low profile to avoid vascular

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### Table 4. Continued

<table>
<thead>
<tr>
<th>Company</th>
<th>Device Name</th>
<th>Specifications</th>
<th>Phasic Development</th>
<th>Potential Advantages</th>
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</thead>
<tbody>
<tr>
<td>Sound Interventions, Sound 360</td>
<td>Catheter Inc, Stony Brook, NY</td>
<td>360° ultrasound energy</td>
<td>SOUND-ITV: FIM trial (n=10); 2 applications/vessel; total energy &lt;2 min per patient; office BP –26.6/–12.5 mm Hg at 3 mo; 24-hour ABPM -23.1/-11.9 mm Hg at 3 mo; Multicenter trial planned for Q1, 2013</td>
<td>No tissue-catheter contact, Single circumferential ablation, Differential dosing of ultrasound energy results in selective nerve ablation with arterial wall sparing</td>
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<tr>
<td>Chemical</td>
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<tr>
<td>Mercator MedSystems Inc, San</td>
<td>Bullfrog Micro-Infusion Catheter</td>
<td>Micro-infusion catheter</td>
<td>Preclinical studies have shown ability to selectively ablate the nerves around the renal artery in a single 20-minute procedure</td>
<td>Procedure potentially &lt;1 h in outpatient setting, No pain, No damage to artery wall, Ability to treat diseased renal arteries, No vasospasm, Ability to treat short or small arteries inaccessible to RF catheters</td>
</tr>
<tr>
<td>Leandro, CA</td>
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<td>Low-pressure balloon (2 atm)</td>
<td>Human investigational studies due to commence</td>
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<td></td>
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<td>Deploys microneedle directly in to the adventitia</td>
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<td>Allows injection of guanethidine in to renal sympathetic nerve sheath</td>
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<td></td>
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<td>6F sheath</td>
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<td></td>
<td></td>
<td>0.014 inch guide wire compatible</td>
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<tr>
<td></td>
<td></td>
<td>Catheters available for &gt;2 mm arteries</td>
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</table>

ABPM indicates ambulatory blood pressure measurement; atm, atmosphere; BP, blood pressure; FIM, first-in-man; and RF, radiofrequency.
access issues; optimal deliverability to often tortuous renal arteries; catheter stability; adaptability to varying arterial calibers; a predictable ablation pattern; speed of application; and availability of therapeutic markers to provide operator feedback.

The EnligHTN Multi-Electrode Denervation System (St. Jude Medical, St. Paul, MN) is perhaps the next most advanced device in the RSDN evolutionary process. The catheter has 4 monopolar radiopaque electrodes over an expandable basket and a deflectable atraumatic tip compatible with an 8F guide. The basket comes in 16 mm (6 mm expansion) and 18 mm (8 mm expansion) sizes. Each ablation takes 90 seconds. The basket can then be collapsed, the catheter pulled back 1 cm, and the basket rotated and expanded, and the ablation sequence repeated. It received CE mark approval in May 2012 and 6-month results from EnligHTN-1, the first-in-man multicenter study, were reported in November 2012. Unlike the Symplicity HTN trials, secondary causes of RHTN were excluded, and diuretic use was mandatory unless previous intolerance was documented. A total of 46 patients (45 were whites and the majority were overweight) proceeded to RSDN with 24-month follow-up planned. The procedure was found to be safe. At 6 months, no patient experienced a reduction in eGFR >50%, doubling of serum creatinine, or progressed to end-stage renal disease. Office BP fell by −26/−10 mm Hg (n=44) and ambulatory BP monitoring by −10/−6 mm Hg (n=44), with one third of patients achieving systolic office BP <140 mm Hg.91

There have also been small series of patients receiving RSDN using standard radiofrequency ablation catheters.92,93 With a variety of specialized equipment either available or in development for RSDN and the entire mechanics of the procedure still in its infancy, it is unlikely this practice will gain much favor.

**Conclusions**

Despite the development of antihypertensive agents with establish efficacy and tolerability, the guideline-driven use of synergistic multidrug regimens, and intensified focus on the modification of contributory lifestyle factors, a significant proportion of patients are still not reaching target BP. Cross-sectional population studies have demonstrated BP control rates of only 30% to 50%94,95; hence the demand for alternative treatment options, such as RSDN, to mitigate the deleterious consequences of treatment-resistant BP.

RSDN has been shown to be both safe and effective, with a durability of action apparently sustained out to 3 years. A recent cost-effectiveness analysis of RSDN based on a Markov model and the Symplicity HTN-2 patient metric has suggested it to be a cost-effective intervention for RHTN, which might also result in lower CV morbidity and mortality.96 Whether the numeric gains in BP reduction translate into prognostic benefit and reduction in CV events remains to be seen. Despite the encouraging preliminary data, the evidence base is small. We must therefore guard against the widespread
proliferation of this technology outside of well-characterized patient cohorts until more is known from both registries and randomized controlled trials. The most fundamental step is to ensure those we are treating with RSDN have true rather than apparent RHTN and that we have been meticulous in excluding secondary causes. Only then we can be sure that RSDN is being used in a judicious and evidence-based manner.

Disclosures

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**Key Words:** apparent resistant hypertension  ◼ radiofrequency ablation  ◼ renal denervation  ◼ sympathetic nervous system  ◼ true resistant hypertension
Renal Sympathetic Denervation Therapy for Resistant Hypertension: A Contemporary Synopsis and Future Implications

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